Endocarditis

Introduction

In clinical practice you will hear people use "endocarditis" colloquially to mean, "bacterial infective endocarditis," and "vegetation" to mean, "the thing growing on the valve is bacterial." That is because infective endocarditis is so much more common than all the other causes of "things on or inflammation of the valves." However, in the pre-clinical sciences and for mastery of this lesson, maintaining strict definitions and delineations is crucial. That is why we repeat the full names of the things we refer to, even though it sounds redundant and you've seen it for the fifth time. This is also why we don't use abbreviations in this lesson: we want you to say the keywords aloud, in full, every time.

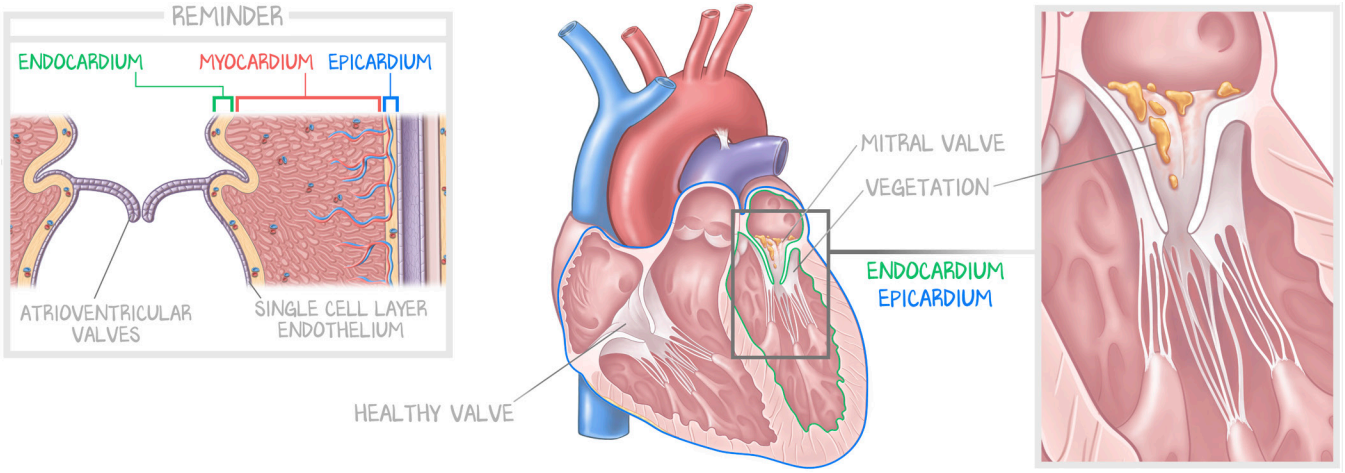

Figure 2.1: Endocardium and Endocarditis
In the last lesson, we taught you about the heart layers—myocardium, epicardium, and endocardium. The endocardium is the innermost lining of the heart chamber—endothelium and its basement membrane and the connective tissue between it and the myocardium. Endocarditis is not simply inflammation of the endocardium. The endocardium is the endothelium. The endocardium also lines the fibrous leaflets of the heart valves. Endocarditis is the formation of vegetations on heart valves.

Endocarditis is **inflammation** (-itis) of the **endocardium**. The endocardium lines the heart chambers and **heart valves**. Every disease discussed in this lesson involves some kind of **vegetation** found **on a heart valve**. The endocardium is more than just the lining of the heart valves, but the general condition named endocarditis means vegetation on a heart valve.

We start with the pathogenesis of an infected vegetation on a heart valve in general (infective endocarditis) and overlapping considerations for all infective endocarditis. Then we spend time building two distinct, nonoverlapping infective bacterial endocarditis illness scripts—acute infective bacterial endocarditis and subacute infective bacterial endocarditis. We close with the noninfective vegetation formations you should be aware of: marantic endocarditis and Libman-Sacks endocarditis. This may feel awkward and foreign, as it's not done this way elsewhere.

Infective Endocarditis

The pathogenesis of infective endocarditis starts with **endocardial injury** secondary to turbulent flow. The endothelium breaks and clotting happens. The specifics are covered in endothelial injury and repair in the Heme/Onc Clotting island. We've included here only what is needed for your comprehension. Some form of nebulous **endothelial injury** occurs, exposing the basement membrane. The first to arrive to help the healing process are platelets, which adhere and aggregate at the site of injury. This is

a temporary and flimsy **platelet plug**. The next to arrive are clotting factors, which use the platelet plug to form a more permanent and stable **fibrin thrombus**. This enables the repair of the endothelium and removal of the thrombus.

If that same process occurs with **organisms circulating in the blood** as well, then when the platelets try to form their platelet plug, the organisms can become trapped, AND the platelets can't do their job quite as well as they're supposed to. A fibrin thrombus attempts to form and serves only to secure the organisms. The immune system notices and **leukocytes** attempt to fight the organisms. Rather than a clean fibrin thrombus from a clean platelet plug and resolution of the injury, the combination of white blood cells, platelets, fibrin, and organisms forms the nidus of the **vegetation**. It grows. The vegetation ends up shielding the organisms from the immune cells, allowing the organisms to multiply and then embolize. A bloodstream infection (bacteremia) is constantly supplied with new organisms shed from the vegetation while new organisms grow underneath. As the vegetation spreads, more and more endothelial cells are claimed.

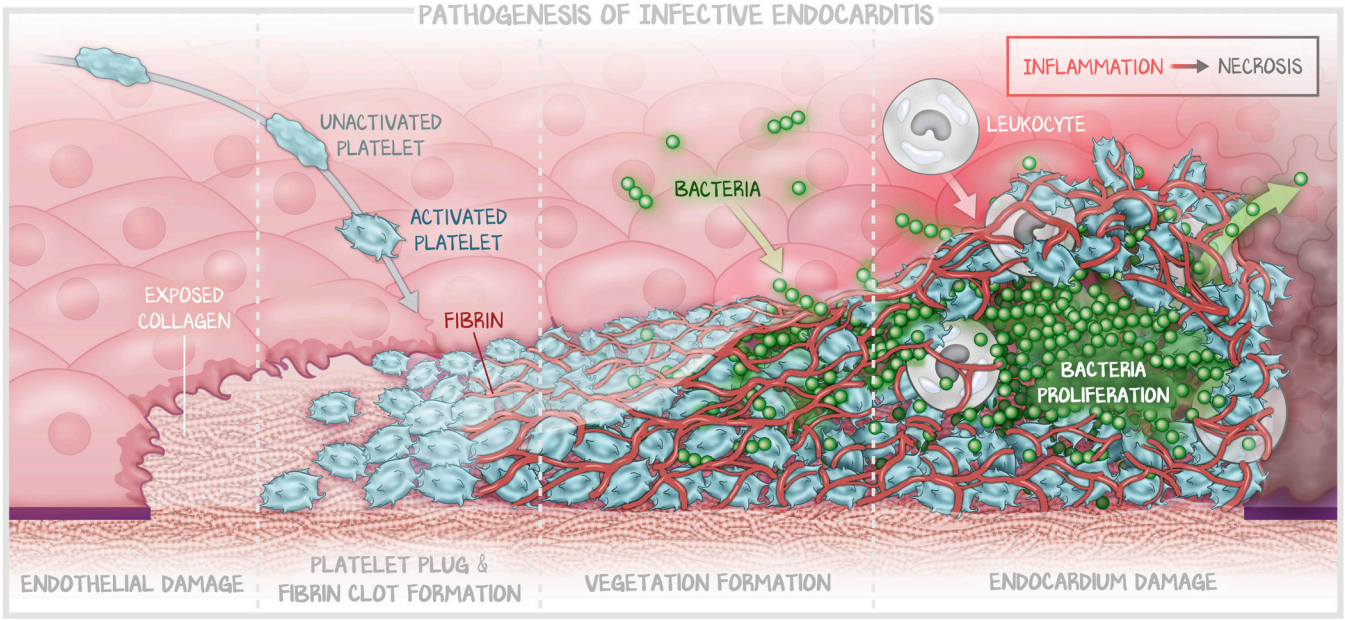

Figure 2.2: Pathogenesis of Endocarditis
Endothelial damage is caused by turbulence. A platelet plug forms and the fibrin thrombus begins to form. Pre-existing bacteremia (bacteria in the blood) during the initial stages of platelet plug or fibrin thrombus formation results in bacteria entrapped in the mass of cells. The mass of bacteria, platelets, and fibrin is called a vegetation. The bacteria proliferate within the vegetation and seed the blood. Immune cells invade the vegetation but are unable to succeed in fighting the infection as the bacteria are shielded from the bloodstream by the fibrin thrombus.

Over 90% of all infective endocarditis occurs on **left-sided valves**. That means almost all bugs, all causes, all comers—almost all occur on left-sided valves. When infective endocarditis is caused by **intravenous drug abuse** (IVDA), it may affect the **tricuspid valve**. The introduction of a needle through the skin and into the vein without first sterilizing the skin site introduces whatever bacteria was on the skin into the bloodstream. The drug gets into the vein, but so do the bacteria on the skin that come along for the ride. Once in the venous system, the bacteria travel to the vena cava, to the right atrium, and through the tricuspid valve. Be careful with causative associations. If there is tricuspid endocarditis, suspect IVDA and look for evidence thereof. If an intravenous drug abuser develops infective endocarditis, it is more likely to be on a left-sided valve.

The symptoms of infective endocarditis are usually taught simultaneously, all at once, in reference to the Duke criteria. We discourage that, but we do show you the Duke criteria. The Duke criteria were established for enrollment in a study and were not meant to be a clinical tool for the diagnosis of infective endocarditis. They are most certainly used that way in clinical practice, but with poor reasoning. This is because the patient is likely to present in one of two distinct ways. Either the patient has **acute infective endocarditis**, which presents with an obvious infection, valve destruction, and blood cultures that won't clear, or they present with **subacute infective endocarditis**, which presents with insidious onset of smoldering inflammatory findings and difficult-to-culture organisms. We strongly recommend that you separate the two presentations as distinct diagnoses and not as the overlap syndrome that the Duke criteria suggest (but be prepared to see it used on the wards this way, as all of your seniors and most of your attendings use the Duke criteria the wrong way). We did not add "bacterial" to the titles of those diagnoses yet, because we haven't talked fungus.

The diagnosis is made with **echocardiography**. A transthoracic echocardiogram (TTE; requires a radiography technician to perform, is not invasive) is less likely to identify a lesion than a transesophageal echocardiogram (TEE; requires a cardiologist to perform, is invasive). After cultures, a TTE is performed, then a TEE if the TTE is negative.

Regardless of the type of organism, treatment is a **minimum of 6 weeks of antibiotics**. There are indications for surgical treatment. If there is **florid heart failure** due to valve destruction or chordae tendineae rupture, surgery is indicated regardless of vegetation size. The other indications are if the vegetation is > 15 mm, regardless of presentation, vegetation > 10 mm with embolization, any fungal endocarditis, or failure of antibiotics. There is **no need to anticoagulate** infective endocarditis.

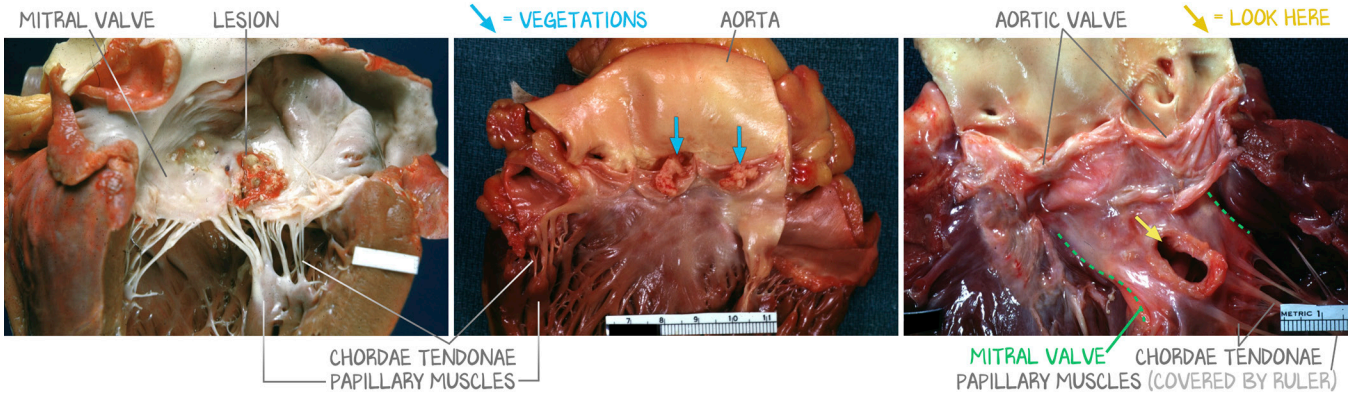

Figure 2.3: Bacterial Endocarditis
(a) Mitral valve demonstrating rheumatic fever changes (chronic) with a single, large bacterial thrombus on the valve leaflets. (b) Aortic valve vegetations on the aorta side of the semilunar valves. (c) No vegetations are visible, but the remnant of one is—the circular defect is a perforation of the mitral valve (it's hard to tell if that is the aortic or mitral valve in this picture).

Prophylaxis to prevent infective endocarditis is considered for people with **bad valves**—congenital defect, prosthetic, rheumatic, previous endocarditis—and those undergoing a procedure with risk for bacteremia, which we call **bad procedures**—dental work, lung surgery, and colonoscopies. The problem is that the recommendations have exceptions. For example, mitral valve prolapse on its own doesn't count as a bad valve. Gastrointestinal and genitourinary procedures that aren't colonoscopies don't count as bad procedures. Here's what you should memorize: previous endocarditis or prosthetic valves require **amoxicillin prophylaxis** for any procedure involving the mouth or the colon.

Acute Infective Bacterial Endocarditis

Acute infective bacterial endocarditis has an **acute presentation** and is caused by **high-virulence** organisms. These organisms are **destructive** (they eat valves and chordae), can affect previously **normal heart valves**, and often present with **large vegetations**. These organisms are **easy to culture**, and cultures are repeated to assess clearance.

Acute infective bacterial endocarditis is most commonly caused by ***Staph. aureus***, a colonizer of human skin. Look for gram-positive, coagulase-positive cocci in clusters. Intravenous antibiotics should clear the bloodstream of infection in less than a day. Another culture 48 hours after the initial culture and the administration of antibiotics should show sterilization of the blood, and the second culture should be negative. *Staph. aureus* endocarditis has the highest likelihood in a patient who presents with bacteremia that doesn't clear.

The effects of acute bacterial endocarditis are sudden and severe. The patient will present with **high-spiking fevers**, **positive blood cultures**, and **evidence of valve destruction**. The bacteria get onto the valves and erode the valve leaflets and chordae tendineae, resulting in regurgitation. A **new regurgitant murmur** and evidence of bacteremia are enough to diagnose acute infective bacterial endocarditis. This can be confirmed with **echocardiography**, which will visualize the vegetation. If the vegetations get large enough, they will **embolize**. Being an acute disease, these are NOT microembolizations (compare with subacute infective bacterial endocarditis, below) but rather **large septic emboli** that compromise arterial supply to distal organs. Originating at the mitral or aortic valve means these septic emboli can go to any organ; originating on the tricuspid valve means these septic emboli go to the lungs. There will be the presentation of acute ischemia of the organ and the presence of abscesses on imaging.

Assessment will reveal the elevation of inflammatory mediators, like ESR and CRP. But given the patient's florid septic picture, assessment is usually not needed.

ACUTE	SUBACUTE
Staph. aureus IVDA Right heart valves	"Strep. viridans" HACEK
Large vegetations	Small vegetations
Valve destruction	No valve destruction
Embolization	No embolization
Easy to culture	Hard to culture
No inflammatory signs	Inflammatory Signs

(TRUNCATED) MODIFIED DUKE CRITERIA	
Major	**Minor**
New regurgitation	Previously damaged valves
Blood cultures with organisms known to cause disease	Fever
Vegetation on echo	Vascular lesions—splinter hemorrhages, Janeway lesions
	Immunological—Osler nodes, Roth spots, rheumatic fever

Table 2.1
Notice how the major criteria reflect the acute presentation, whereas the minor criteria reflect the subacute presentation. Learn the illness scripts for the two severities of bacterial infective endocarditis, and leave the checklists to the researchers and bureaucrats.

Subacute Infective Bacterial Endocarditis

Subacute infective bacterial endocarditis is still an infection of a heart valve secondary to bacteremia, but the presentation is much more subtle, which is why it's called subacute. It presents insidiously because the infection is with insidious bacteria. These are low-virulence organisms, so they require a **previously damaged heart valve**—prosthetic valve, congenital defect, rheumatic disease, or previous endocarditis—and present with **smaller vegetations**. These organisms are **difficult to culture** but are also less likely to cause valve destruction or embolization. Repeated cultures are required to identify the organism.

The presentation is more **gradual**, developing insidiously over weeks to months. It is less a syndrome of infection (there is no sepsis) and more of a **smoldering inflammation**. Students classically think to look for a fever, the absence of which they assume makes infection less likely. In smoldering inflammation, there may be no temperature elevation at all, periods of elevated temperature that clear spontaneously, or even frank fevers that seem to resolve with over-the-counter antipyretics. The point is, it won't be an obvious fever that doesn't ever go away. Instead, there will be fatigue, weight loss, and nonspecific symptoms. Assessment reveals modestly elevated inflammatory mediators (CRP and ESR). The duration of onset is weeks to months, and the modest elevation of inflammation can provoke **anemia of chronic inflammatory disease** (high ferritin, low TIBC; see Hematology/Oncology: Anemia #4: *Approach to Anemia*).

Embolization can occur in subacute infective bacterial endocarditis, but not in the same way as in acute infectious bacterial endocarditis. **Microembolizations** and **immune complex vasculitis** define the classic physical exam findings. Microembolizations include **splinter hemorrhages** (linear hemorrhages in the nail beds) and **Janeway lesions** (painless areas of hemorrhage on the palms and soles of feet). Immune complex vasculitis lesions are O**sler nodes** (vasculitis on the tips of toes and pads of fingers and are "Ouch!" painful) and **Roth spots** (retinal hemorrhages shown as an irregular red area with a central white dot).

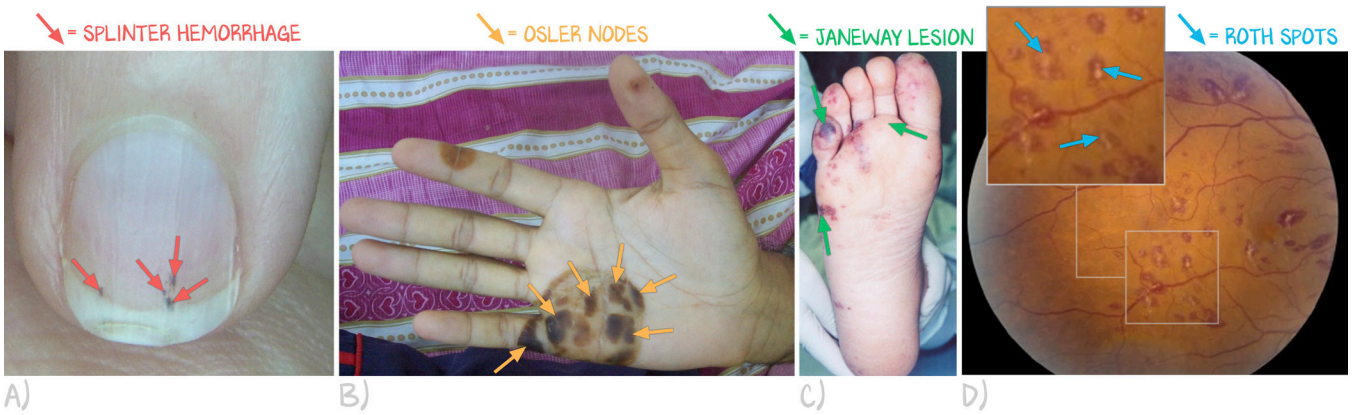

Figure 2.4: Subacute Bacterial Infective Endocarditis
(a) Splinter hemorrhages are linear hemorrhages in the nail bed. (b) Janeway lesions are painless hemorrhages on the palms. (c) Osler nodes are painful vasculitis nodes on the pads of the digits. (d) Roth spots with white dots and hemorrhages around them.

The most common organisms belong to **viridans group strep**, the strep of the mouth. However, you should associate this disease with the **HACEK** organisms—the most difficult to culture. There will be no suspicion of infection because there is no acuity and no high fevers. The diagnosis is suggested by the physical exam findings. **Culture multiple times without giving antibiotics.** Start antibiotics only after you have identified the causative organism.

BUG	ASSOCIATION
"Strep. viridans"	Found in the mouth, gotten from dental procedures without prophylaxis.
Strep. gallolyticus (*Strep. bovis* type 1)	Found in the colon, can be gotten from a colonoscopy. But IF *Strep. bovis* bacteremia or *Strep. bovis* endocarditis, then worry about colon cancer and get a colonoscopy.
Staph. epidermidis	Produces adherent biofilm and causes endocarditis of prosthetic heart valves.
Candida	*Candida* fungemia comes from TPN. Fungemia can seed the valves, tricuspid.
HACEK	*Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella*. Extremely difficult to culture; three blood cultures without antibiotics.

Table 2.2: Organisms
Associations of organisms and virulence.

Nonbacterial Thrombotic (Marantic) Endocarditis

In marantic endocarditis, the endothelium gets damaged. A clot forms. **NO ORGANISMS** get in. The entire vegetation is just **platelet-fibrin aggregates and immune complexes**. The pathogenesis is just like in bacterial infective endocarditis, only there aren't any organisms. Marantic endocarditis is almost always found on the **mitral valve** and caused by a **paraneoplastic** syndrome that provokes a **hypercoagulable state** and can affect **normal valves** as well as damaged ones. This hypercoagulable state is typically caused by circulating mucin from mucin-producing tumors of the pancreas or colon. The vegetations are **nondestructive** and **multiple**. Because they occur on the lines of closure, they may result in poor coaptation, resulting in regurgitation. These are able to **embolize**. To prevent embolization, **anticoagulation** is indicated. However, more often than not, these lesions are discovered on autopsy, the patient having died from the cancer that induced them.

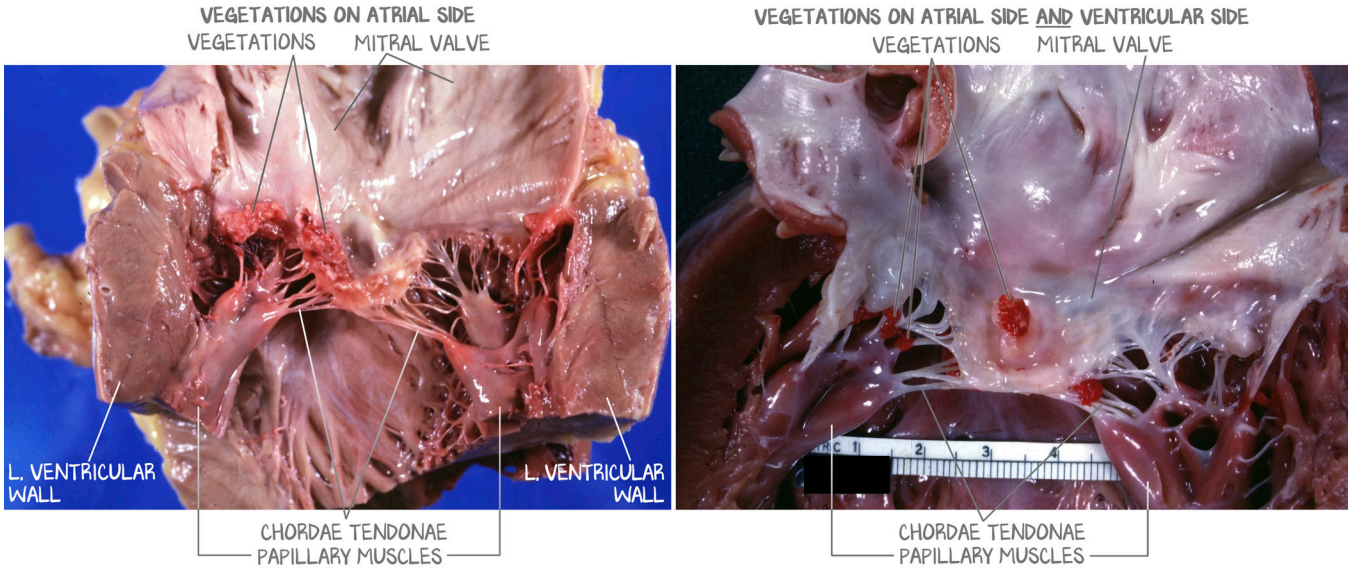

Figure 2.5: Nonbacterial Thrombotic Endocarditis
(a) Marantic endocarditis demonstrating noninfective, thrombus-only vegetations on the mitral valve leaflets on the atrial side only, and near the leaflet edge. (b) Libman-Sacks endocarditis demonstrating vegetations on either side of the mitral valve.

Libman-Sacks Endocarditis

Libman-Sacks endocarditis (LSE) gets an abbreviation in the first place because it is an eponym, but more importantly, because **LSE is found in SLE**. Patients with systemic lupus erythematosus can develop Libman-Sacks endocarditis. Essentially eradicated since the advent of steroids, this form of endocarditis is unique in that it forms vegetations on **both sides of the mitral valve**. LSE does not necessitate treatment with anticoagulation. However, LSE was found almost exclusively in patients with the form of lupus that also has antiphospholipid antibody (APLA) syndrome, which does, on its own, necessitate anticoagulation.

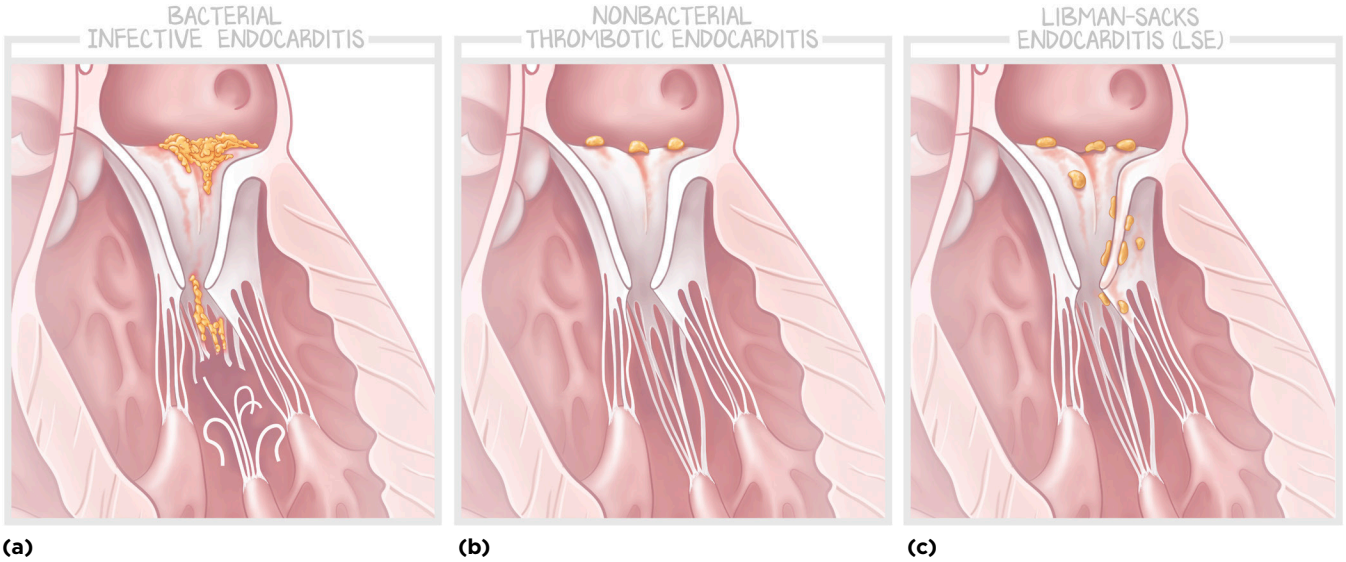

Figure 2.6: Comparison of Endocarditis Types
(a) Acute bacterial infective endocarditis with the destruction of valve leaflets. (b) Marantic endocarditis with smaller vegetations on one side of the valve. (c) Libman-Sacks endocarditis with small vegetations on both sides of the mitral valve.

Citations

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